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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/998,832	11/29/2001	Robert Chow	020035-001100US	7166

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EXAMINER	
SHUKLA, RAM R	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 02/13/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/998,832	CHOW ET AL.	
	Examiner	Art Unit	
	Ram R. Shukla	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 October 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-26* is/are pending in the application.

4a) Of the above claim(s) *3-9 and 11-13* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,10 and 14-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *29 November 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *3/21/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. Applicant's election with traverse of the invention of group VI, drawn to a method of preventing or treating HIV infection by screening for stem cells that have a beneficial gene that alters the ability of HIV to infect cells and transplanting said cells into a patient, wherein said beneficial gene encodes a receptor or co-receptor for HIV entry, wherein said receptor is CCR5 claims 1, 2, 10, 14-17 and 18-26 in Paper filed 10-20-2003 is acknowledged. The traversal is on the ground(s) that all the inventions stem from a common concept and theory and are thus relate. This is not found persuasive because even thought they may be based on a concept, they are patentably distinct, will require separate search in the art and both search and examination of all the inventions will be a burden. Applicants arguments that examiner must show burden of searching by separate classification and have acquired status in the art. These arguments are not persuasive because classification is a very broad grouping of inventions and very distinct and different inventions are present in a particular class/subclass. Additionally, the different inventions have different status in the art because they are drawn to a method of treatment based on the expression of certain cellular receptors which have very different structure and function.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 3-9, 11-13 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper filed 10-20-2003.

3. Claims 1, 2, 10, 14-26 drawn to a method of preventing or treating HIV infection by screening for stem cells that have a beneficial gene that alters the ability of HIV to infect cells and transplanting said cells into a patient, wherein said beneficial gene encodes a receptor or co-receptor for HIV entry, wherein said receptor is CCR5 claims are under consideration.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention, if not, whether an artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue" (In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)).

Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification, therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of the invention, therefore skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

Claimed invention encompasses a method of preventing or treating HIV infection by first screening of plurality of cells of any origin for stem cells that have a beneficial gene and then transplanting these cells into a patient thereby preventing or treating HIV infection. Dependent claims limit the beneficial gene to a polymorphism of proteins expressed in immune cells and that the protein is a receptor or co-receptor for HIV entry in a cell, the co-receptor being CCR5 and the polymorphism being deletion of a 32 base pair region in the coding region or the promoter region of CCR5. Other claims recite that the stem cells are typed for HLA by certain method and the stem cells are screened by a certain method and that the stem cells are treated to express a non-native HLA protein or to inhibit expression of native HLA protein.

The specification as filed does not provide sufficient guidance to isolate the cells and use them in treating or preventing HIV infection in a patient and an

artisan of skill would have required undue experimentation to practice the claimed invention because the art of HIV prevention or treatment was unpredictable at the time of the invention and neither the art of record nor the specification provide guidance to practice the claimed method as discussed below.

The specification as filed discusses the state of the art that the known HIV resistance genes are polymorhic form of CCR5 and CXCR4 coreceptors and of SDF1 promoter, RANTES promoter, IL-10 promoter. The specification also states that HLA alleles also influence HIV-1 disease progression (see pages 1-2 of the specification). The specification also states on page 3:

> [09] The discovery that certain polymorphisms confer resistance to HIV has led to the proposal of therapies which repopulate the immune system with cells more capable of resisting infection and/or more capable of neutralizing the virus. By preventing *de novo* infection of cells, such therapy can eliminate the need for prolonged treatment with inhibitors of viral replication. Furthermore, the specific nature of such therapies should reduce side effects.

This clearly indicates that at the time of the filing of the instant application, the treatment with certain polymorphisms that conferred resistance to HIV was a hypothesis and the art of record did not teach how to treat or prevent HIV infection using these polymorphisms.

Rest of the specification is a disclosure of general molecular biology methods and techniques, but there is no specific guidance for treating HIV infection in a patient as recited in the claims. Figure 1 is flow chart, again of general steps, without any specifics. The methodology for transplantation of stem cell rich cell population into patients and therapeutic applications has been described in two paragraphs each, again comprising general statements and lacking any specific information. In summary, the specification does not provide any specific teaching for practicing the claimed method and does not teach any working examples for treatment or prevention of HIV in patients. It is noted that the specification neither teaches any working example in an animal model nor it teaches method for treating human patients.

At the time of the invention, as discussed in the specification, the art reported correlation of HIV co-receptor CCR5 polymorphism in HIV infected patients with disease progression (eg. see McDermott et al. The Lancet 352:866-870, 1998; Roman et al. HIV Clin. Trials 3: 195-201, 2002), however, the art of record did not teach how to treat or prevent HIV infection in a patient by transplanting stem cells that have the protective polymorphism. In fact there were contradictory reports in certain instances where the CCR5 polymorphism did not provide protection, rather it caused acceleration of disease (see last paragraph in the right column on page 195 continued on page 196). Therefore, at the time of the invention there was no evidence of treating or preventing HIV infection in a patient by transplanting stem cells with any beneficial gene polymorphism and treatment of a HIV infection or prevention of HIV infection would have been unpredictable since a number of factors played role in the process of blocking infection (see the last paragraph in the left column of page 1317 and the specification does not teach as to how these auxiliary factors or other polymorphic proteins would have been provided to a patient. Claims 11-15 list CD4, CCR2, CCR2-641 and CCR5, however, the art does not provide sufficient teachings as to what polymorphisms would make a patient HIV infection resistant or treat HIV infection. In fact it has been reported that polymorphism in the promoter region of CCR5 increases HIV infectivity. Stephen O'brien and Michael Dean in review in Scientific American (September 1997), proposed destroying all HIV infected blood cells in a patient and then rescuing the patient with the bone marrow from donors who are homozygous for the deletion mutant of CCR5 and they discussed the limitations of the method and the finding that some individuals homozygous for CCR5 mutant got infected with HIV and predicted that any preventives or therapies aimed at blocking HIV's access to CCR5 could backfire and encourage, instead of forestall, infection and advancement to AIDS (see 50 and 51). This clearly establishes the unpredictability of the method of treatment of HIV infection or HIV infection prevention and the specification does not add to cure these deficiencies by providing any teachings for practicing the claimed method. The specification does not provide any guidance as to how would an artisan decide which polymorphism will be beneficial. Additionally, specification

does not teach what polymorphism of CD4 would be beneficial since CD4 is the most common and efficient HIV infection in a T lymphocyte.

It is noted that while the specification discusses the known polymorphisms reported in the art, it does not provide how would an artisan screen for any other beneficial gene or what parameters will describe a beneficial gene or how would an artisan isolate a stem cell that has a beneficial gene with a certain polymorphism other than the polymorphism of certain genes reported in the art. The specification does not provide any guidance regarding the characteristics of the mutation or polymorphism that could be used for identifying a beneficial gene and screen a stem cell that expressed the beneficial gene. The specification on page 10 describes a general method of hybridization and immunological methods, but does not provide any specific guidance regarding the characteristics of probe to be used in the hybridization or immunological method. The specification does not provide any specifics or determinants as to what will be considered a beneficial gene. It is noted that at the time of the invention while the art taught to screen for PBMC, CD3+ cells, CD4+ lymphocytes and CD4+ monocytes or other blood types for the expression of a gene, the art did not teach how to screen for a stem cell from which all differentiated cells would have a certain polymorphism. For example, earlier studies in the art (see Shieh et al. International Immunology 12: 1311-1318, 2000, page 1313, first full paragraph in the right column) indicated that only a certain percent of PBMCs expressed surface CCR5 and there was decreased average protein quantity in individuals heterozygous for CCR5delat32. Neither the art nor the specification teaches what amount of a beneficial gene comprising stem cell will be required to treat or prevent HIV infection.

The specification does not teach how to isolate the stem cells with a beneficial gene and expand them ex vivo or in vivo in an amount sufficient for transplantation. At the time of the invention, ex vivo expansion of hematopoietic stem and progenitor cells in general was unpredictable (see the entire article by Srour et al. The Journal of Hematotherapy 8:93-102, 1999, particularly page 97) and it was not routine in the art to in vivo expand stem cells for transplantation in patients. Since in the instant case the stem cells will have a particular mutation in a

receptor or co-receptor gene, it would be unpredictable what kind of culture conditions would be required to expand and maintain the stem cells in vitro. It is noted that while the art teaches that CCR5 delta 32 mutant may make a cell resistant to HIV infection, it does not provide any guidance for culturing and maintaining a stem cell expressing the mutant CCRE5 or any other beneficial gene and it is unpredictable whether such a stem cell would be viable in vitro and what would be the role of a mutant gene in the survival of the cell in vivo or ex vivo.

The specification does not provide any guidance regarding the patient in which the stem cells be transplanted, for example, what would be the state of the endogenous stem cells that would be already infected with HIV or that would be susceptible to HIV infection because if the patient still has the infected cells or the HIV infection susceptible cells, the patient will still be infected with HIV. The specification does not teach as to how will the endogenous stem cells and cells of a HIV infected patient or a patient will be depleted and will be prevented from repopulating the hematopoietic cells of a patient.

Next the claimed invention as recited will encompass autologous, allogeneic as well as xenogeneic transplantation, however, these transplantation methods are not routine. For example, Fred Gage (Nature 392:18-24, 1998) noted that for non-autologous cells, the most serious challenge is the destruction of cell implant by the host's immune system and that in xenografts; complement mediation is the major problem whereas the hyperacute rejection is the rapid and dramatic immunological response. The specification does not teach how to address the issues of hyperacute and complement mediation associated with the xenotransplantation of cells.

At the time of the invention, xenogeneic transplantation of any cells was not routine. Samstein et al (Samstein et al. Journal of American Society of Nephrology 12:182-193, 2001), reviewing the state of the art of physiologic and immunologic hurdles of xenotransplantation, summarized:

"Although the potential advantages of xenotransplantation generate enthusiasm, these advantages must be weighed against what may seem to be the daunting hurdles to the clinical application of xenotransplantation. These hurdles

include the immune response of the recipient to the transplant, the physiologic limitations of the transplant, infection, and ethical concerns".

In summary at the time of the invention, the art of xenotransplantation was unpredictable and the specification does not provide any guidance how to address the issues of unpredictability in xenotransplantation of bone marrow cells. It is emphasized that the specification does not provide any guidance as to how would the transplantation of any stem cells would have been carried out.
Claim 18 recites that the source of the cells for screening is umbilical cord blood. The specification does not teach how the cells will be screened from an umbilical cord blood sample, identified, isolated and expanded ex vivo or in vivo.

Therefore, in view of the breadth of the claims and the lack of guidance provided by the specification as well as the unpredictability of the art, one of ordinary skill in the art at the time of the invention would have required an undue amount of experimentation to screen stem cells with beneficial genes and transplant them in a patient to prevent or treat HIV infection. It is noted that the unpredictability of a particular area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See Ex parte Singh, 17 USPQ2d 1714 (BPAI 1991).

4. Claims 1, 2, 10, 18-26 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claimed invention encompasses a method of preventing or treating HIV infection by first screening of plurality of cells of any origin for stem cells that have a beneficial gene and then transplanting these cells into a patient thereby preventing or treating HIV infection. Dependent claims limit the beneficial gene to a polymorphism of proteins expressed in immune cells and that the protein is a receptor or co-receptor for HIV entry in a cell.

When the claims are analyzed in light of the specification, instant invention encompasses any beneficial gene, any stem cell, and polymorphism of any

beneficial gene in coding or promoter of gene, any receptor or co-receptor for HIV entry in a cell. In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been described by their complete structure. In the instant cathe the specification discloses chemokine receptors, IL-10, SDF-1 and HLA (see specification on pages 1-3). However, the specification does not provide any disclosure as to what would have been the structure of a representative number of species of the claimed broad genus which encompasses any gene that increases or decreases disease progression (see page 5, [23]. Next, then, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics (i.e. other than nucleotide sequence), specific features and functional attributes that would distinguish different members of the claimed genus. In the instant case, the specification does not provide any specific identifying characteristic for a representative number of species of the claimed genus. The specification does not teach the structure and identifying characteristics of a sufficient number of representative species of HIV receptor or co-receptors and the stem cells that would express such receptors or co-receptors or the beneficial genes as recited.

Applicants' attention is directed to the decision in *In re Shokal*, 113 USPQ 283 (CCPA 1957) wherein is stated:

> It appears to be well settled that a single species can rarely, if ever, afford sufficient support for a generic claim. In re Soll, 25 C.C.P.A. (Patents) 1309, 97 F.2d 623, 38 USPQ 189; In re Wahlforss et al., 28 C.C.P.A. (Patents) 867, 117 F.2d 270, 48 USPQ 397. The decisions do not however fix any definite number of species which will establish completion of a generic invention and it seems evident therefrom that such number will vary, depending on the circumstances of particular cases. Thus, in the case of small genus such as the halogens, consisting of four species, a reduction to practice of three, or perhaps even two, might serve to complete the generic invention, while in the case of a genus comprising hundreds of species, a considerably larger number of reductions to practice would probably be necessary.

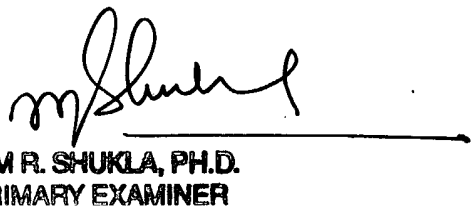
In conclusion, this limited information is not deemed sufficient to reasonably convey to one skilled in the art that Applicant was in possession of the claimed broad genus at the time the application was filed. Thus it is concluded that the written description requirement is not satisfied for the claimed genus.

5. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ram R. Shukla whose telephone number is (571) 272-0735 . The examiner can normally be reached on Monday through Friday from 7:30 am to 4:00 p.m. If attempts to reach the examiner by telephone are

unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached at (571) 272-0734. The fax phone number for TC 1600 is (703) 703-872-9306. Any inquiry of a general nature, formal matters or relating to the status of this application or proceeding should be directed to the William Phillips whose telephone number is (571) 272-0548.

Ram R. Shukla, Ph.D.
Primary Examiner
Art Unit 1632



RAM R. SHUKLA, PH.D.
PRIMARY EXAMINER